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Review Article

Epigenetic of Aerobic Exercise and the Aging Processes

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Abstract

Aging is commonly defined as the accumulation of diverse deleterious changes occurring in cells and tissues with advancing age that are responsible for the increased risk of disease and death. Physical inactivity that typically occur in aging also decrease maximal oxygen uptake. Successful aging is a function of both genetic and environmental factors. The primary aging process, itself genetically associated, occurs both independently of life style and in the absence of disease. No matter what genes one has inherited, the body is continually undergoing complex biochemical reactions. Some of these reactions cause damage and, ultimately, aging in the body. Studying these complex reactions is helping researchers understand how the body changes as it ages. Chemically speaking the process is slow and complicated, but over time more and more protein molecules are cross-linked. These cross-linked molecules do not function properly. When enough cross-linked molecules accumulate in a specific tissue (such as cartilage, lungs, arteries and tendons), there can be a change in function. In addition, Alteration may contribute to the accumulation of deleterious macromolecules and altered membranes and organelles in cells. Non-coding RNAs like lncRNA or microRNAs, can help to explain how cells with identical DNA can differentiate into different cell types with different phenotypes. However, the basic mechanism by which exercise activates genes involves a stimulus signal to the DNA, then transcription via messenger RNA, and finally translation into protein. In addition, data suggests that the epigenetic pattern may change during aging, affecting key genes' targeting of age-related DNA methylation. Thus, age can influence DNA methylation, gene expression and subsequently in vivo metabolism. Though, chronic aerobic exercise significantly impact positively DNA methylation, in a muscle tissue and gene-specific manner. Untrained and trained elderly can increase the response of the central factors, i.e. cardiopulmonary without a significant reduction in arterial-venous oxygen differences. In elderly subjects, skeletal muscle mitochondrial, tissue blood flow and oxygen exchange capacities are well matched. It seems that intrinsic mitochondrial function and regulation are not altered significantly. In addition, exercise has a role in angiogenesis, neurogenesis, learning and cognition. The above data indicates that the older person's skeletal muscle, cardiovascular system and pulmonary function retain a high degree of trainability, with much of the improvement occurring peripherally just as in younger individuals.

Keywords: Aging; DNA Methylation; Epigenetic; Oxygen Uptake; Oxygen Delivery; Oxygen Extraction; Mitochondria

Introduction

Aging is a complex multi-factorial process that not only involves the natural processes of aging, but also the increased risk for different diseases – coronary heart disease, diabetes and cancer [1]. Studies have demonstrated that genetics can play a major role in aging. When researchers adjust the genes in certain mice, yeast cells and other organisms, they can almost double the lifespan of these creatures. Successful aging is a function of both genetic and environmental factors [2]. The primary aging process which is genetically associated, occurs both independently of life style and in the absence of disease [3]. Aging-related changes occur mainly in the cardiopulmonary and skeletal muscles, bringing about a reduction in physical performance [4]. Maximal work capacity is decreased with aging regardless of lifestyle because of genetic factors. Consequently, the maximal oxygen uptake (VO2max) decreases. Such consequences contribute to the geriatric syndrome of frailty, thereby severely limiting the function, quality of life and longevity [5]. Apart from genetic endowment, an individual must also interact with environmental factors associated with longevity. One of these factors includes maintaining high level of physical activity [6]. Chronic endurance training will attenuate the decline in VO2max associated with age [3,7].

The basic mechanism by which exercise activates genes (epigenetic) involves a stimulus signal to the DNA, then transcription via messenger RNA, and finally translation into protein [8,9]. Data further suggests that the epigenetic pattern may change during aging, affecting key genes [10] targeting age-related DNA methylation [11]. While DNA methylation is increased in skeletal muscle of elderly compared with young, the opposite pattern is found for gene expression [11]. Additionally, the transcript level of DNA methylation in skeletal muscle is associated with increased VO2max in vivo [11]. These data demonstrate how age can influence DNA methylation, gene expression and subsequently in vivo metabolism. However, chronic aerobic exercise training significantly impact positively DNA methylation and left ventricular growth in young males associated with ACE I/D polymorphism. The role of genetics in determining exercise performance is best viewed at different levels of influence. The very nature of genetics is based on the expression of genetic information (i.e. from genes) that directs the cellular development of an organism. In humans, it is possible to illustrate cellular genetic regulation in the type and concentration of certain enzymes in skeletal muscle, which in turn influences the metabolic capacity of the muscle, influences adaptability to training and determine the potential to excel during exercise. However, this review will focus on the influence of exercise on genetics and thus, aging. Epigenetic and metabolism VO2max is one of the main variables in the field of exercise physiology, and is frequently used to indicate the fitness level of an individual [12]. At maximal exertion, oxygen extraction can reach values of 140–180 mLO2•L-1 blood [13].

Age causes structural and functional changes in cardiovascular, oxygen extraction ability and skeletal muscles in humans, bringing about a reduction in aerobic power and physical performance [14,15]. The lowest rates of decline in VO2max with age are found in those who remain disease free and continue to maintain high levels of aerobic training [16]. No significant decline in the VO2max over a 10 year period was found in a group of competitive master athletes who maintained their training intensity and continued to compete. It has been suggested that the longitudinal decline in VO2max in older male endurance athletes is highly dependent upon the continued magnitude of the training stimulus [3], whether maximal oxygen delivery to the working muscles actually decreases with primary aging depends on many interactive factors. First, the primary aging process, which has a genetic component, occurs in the absence of disease and independent of life-style [17].

Aerobic exercise induces several metabolic adaptations to meet increased energy requirements. Promoter DNA methylation, histone post-translational modifications, Non-coding RNAs like lncRNA or microRNA expression are involved in the gene expression changes implicated in metabolic adaptation after exercise. Although there is no uniform definition of epigenetics, it has the potential to explain various biological phenomena that have before now defied complete explication. It is series of chemical tags that modify DNA and its associated structures constitute the epigenome, and include any genetic expression modifier independent of the DNA sequence of a gene. However, it does not involve changes in the nucleotide sequences [18]. Epigenetic modifications and many epigenetic enzymes are potentially dependent on changes in the levels of metabolites, such as oxygen, tricarboxylic acid cycle intermediates, 2-oxoglutarate, 2-hydroxyglutarate, and β-hydroxybutyrate, and are therefore susceptible to the changes induced by exercise in a tissue-dependent manner. Most of these changes are regulated by important epigenetic modifiers that control DNA methylation (DNA methyl transferases, and ten-eleven-translocation proteins) and post-translational modifications in histone tails controlled by histone acetyltransferases, histone deacetylases, and histone demethylases [19]. In addition to restructuring the muscular and skeletal system to better handle mechanical stress during effort, aerobic exercise also affects gene expression with respect to metabolism. The effects are widespread and can affect anything from muscle growth to aerobic stamina to diabetes and other metabolic disorders [20]. In general, even a small amount of exercise can induce hypo-methylation of the whole genome within muscle cells. This means that many regulatory genes can be turned on for pathways like muscle repair and growth. The intensity of the exercise directly correlates to the amount of promoter demethylation, so more strenuous exercise activates more genes [20].

Class IIa Histone deacetyltransferases (HDACs) are highly expressed within human skeletal muscles. HDACs and acetyltransferases control the epigenetic regulation of gene expression through modification of histone marks. Chromatin remodeling by the post-translational modification of histones is thought to be a central mechanism for the epigenetic regulation of gene expression [21]. Exercise helps to reduce HDACs' activity, especially at promoters, which affects

gene expression. In mice, this regulation of HDACs has been shown to increase the amount of type I fibers in muscle. The amount of type I fibers is positively correlated with the maximal aerobic capacity and fat metabolism. Type I fibers are slow twitch, endurance fibers that aging (57-76 years age range) does not impair the muscle angiogenic response to exercise training [22].

Exercise epigenetic

Epigenetic factors include DNA methylations, histone modifications, non-coding RNAs like lncRNA or microRNAs, can help to explain how cells with identical DNA can differentiate into different cell types with different phenotypes. Some interface of aging and energetic were identified, these included: genes that accelerate aging or in contrast promote longevity in model organisms, DNA damage responses and telomeres, molecular mechanisms of life span extension by calorie restriction and pharmacological interventions into aging [23].

Epigenetic mechanisms affected by physical exercise have also been seen to be involved in age-related processes. A major component of aging is significant loss of DNA methylation over time [24]. Methyl deoxycytidine, which is a methylated cytosine on the 5' carbon of a cytosine, is involved in the process of cell differentiation and maintenance. Cell differentiation involves methylation of different areas within the DNA of a cell, which can alter the transcription of genes. During cell differentiation, DNA methylation is important for establishing the identity and function of a cell because of its role in controlling gene expression. As one ages, the amount of DNA methylation slowly begins to decrease. Recent study [25], looking at genome epigenetic of children and older individuals suggests that the older individuals had significantly decreased overall DNA methylationIn and histone. These mechanisms include permanent structural changes to the organ caused by suboptimal levels of an important factor during a critical developmental period, changes in gene expression caused by epigenetic modifications (including DNA methylation, histone modification, non-coding RNAs like lncRNA or microRNAs) and permanent changes in cellular ageing. Studies have also looked at methyl deoxycytidine residues from tissues collected from rodents at various ages. These studies found that DNA methylation loss increased significantly as the rodent aged (24). A major component of aging is significant loss of DNA methylation over time [24,26], thus, aging rate is related to a reduction in DNA methylation activity [28].

This loss of DNA methylation appears to be slowed by physical exercise. Further studies have looked at the effects of aerobic exercise on DNA methylation and aging in humans, revealing that genome with DNA methylation in adult individuals who obtained thirty or more minutes of exercise a day had significantly more DNA methylation as compared to sedentary individuals [27,28]. Such exercise has been shown to induce positive changes in DNA methylation within adipose tissue and regulate metabolism in both healthy and diseased individuals [29,30]. Increased DNA methylation of genes Hdac4 and Ncor2 has also shown to increase lipogenesis following exercise [27,29]. Consequently, aerobic exercise affects aging rate through slowing the pace of the DNA methylation loss over time.

All these epigenetic alterations may have clinical relevance, thus playing an important role in the prevention and confrontation of neurophysiological disorders, metabolic syndrome, cardiovascular diseases and cancer. Acute exercise is associated with DNA hypomethylation of the entire genome in skeletal muscle cells of sedentary individuals and high intensity exercise tends to cause reduction in promoter methylation of certain genes [30].

In human skeletal muscle the expression of many genes tends to increase or decrease between the third and seventh decades. The changes are modest when averaged over all of the cells in the tissue [31]. Exercise differentially influences sarcoplasmic reticulum calcium-ATPase isoform expression in type I and type II fibers. Additionally, adenosine monophosphate-activated protein kinase- α2 influences the regulation of sarcoplasmic reticulum calcium-ATPase2a mRNA in type I skeletal muscle fibers following exercise training [32].

It is estimated that an average of 10 transcription units, the vast majority of which make long noncoding RNAs (lncRNAs), may overlap each traditional coding gene. [33]. Noncoding RNAs (ncRNAs), including microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), have emerged as a class of previously unrecognized transcripts. They are emerging as integral components of the gene regulatory networks in a broad range of biological processes, and dysregulation of their expression has been implicated in many human diseases [34,35]. Following aerobic exercise skeletal muscle's myosin heavy chain gene expression (contractile ability) was altered. Muscle fiber type I and IIa myosin heavy chain mRNA was increased by 11%, while type IIb was decreased by 38% [36]. In addition, insights to myosin heavy chain regulatory mechanisms previously suggested that in rats lncRNA are conserved in humans [36]. It has been discovered that MicroRNAs (miRNAs) plays important roles in immune function and often act to attenuate or silence gene translation. miRNAs interfere with mRNA that is present and render it unusable and therefore decrease the product of that mRNA. miRNAs regulate many physiological processes, such as inflammation, angiogenesis, as well as ischemia. miRNA expression profiling of various human myopathies identified a common set of miRNA that were up-regulated in each of the different muscular disorders [37]. Drummond and colleagues reported that let-7 miRNA expression was elevated in skeletal muscle of older humans [38]. The significance of this finding is that let7 expression may be a contributing factor to the alteration in satellite cell activity observed with age.

Aerobic exercise training has been established as an important phenotype capable of altering the human skeletal muscle. In healthy subjects after aerobic exercise training can thus locally modulating some signaling ways in muscle regeneration [39]. It reduces the overall number of various

miRNAs within the skeletal muscle that produce negative effects and increase myomiRs expression with its positive effect on the muscle reconstruction [37]. Stimuli that cause the body to enter an anabolic, or constructive, phase, such as resistance training as well as the correct diet, have also shown a reduction of miRNAs. This reduction may actually play a role in the growth of the muscle cell [20]. Exercise is also known to positively influence the expression patterns of miRNAs in leukocyte cells. It is associated with rapid changes in the profile of gene expression in circulating neutrophils [40].

Telomere shortening

Another component of aging is the gradual shortening of telomeres located at the end of chromosomes. Telomere length regulates gene expression long before telomeres become short enough to produce a DNA damage response thus the main role of telomeres is a tumor suppressor mechanism [41]. Rapid telomere shortening may indicate a cellular hyper-activation, hyper-proliferation and/or hyper-secretary phenotypes often associated with cellular senescence, stem cell exhaustion and diseases of aging [41]. Endogenous human genes can be regulated by the length of telomeres prior to the onset of DNA damage signals, and suggest the possibility that cell turnover/telomere shortening may provide a mechanism for adjusting cellular physiology. The up regulation of ISG15 with telomere shortening may contribute to chronic inflammatory states associated with human aging [42]. Mammalian telomeres are formed by tandem repeats of the TTAGGG sequence, which are progressively lost with each round of cell division. Aging and age-related diseases are associated with the significant shortening of these sequences. The shrinking of telomeres occurs in somatic cells where telomerase, the enzyme in control of telomere lengthening, is not expressed [43]. However, it has been seen that telomeres can transcribe non-coding RNA, or functional RNAs that do not get translated into protein. These non-coding RNAs can be positively impacted by physical exercise. A study found that mice exposed to short-term running phases had increased non-coding RNA transcription at telomeres as compared to sedentary controls [44]. This increase in non-coding RNA transcription aided telomere stability, making the exercise group's telomeres less likely to be as affected by aging over time.

Angiotensin-converting enzyme

Measuring genetic markers centered on the renin-angiotensin system (ACE) and identification of candidate genes revealed that different molecular mechanisms are responsible for the different types of left ventricular mass increases seen in athletes and in cardiac patients [45]. Kasikcioglu and colleagues [46] suggested that exercise-induced left ventricular growth in young males is strongly associated with ACE I/D polymorphism. In addition, the absence of the D allele from the 287-base pair marker in the angiotensin converting enzyme gene resulted in a higher than normal ACE level. Following a 10-week physical training period in male military recruits, echocardiographic measurements of left ventricular mass revealed that persons with D allele in the 287-base pair marker in the ACE had a mixed cardiac response to military basic training, with both eccentric and concentric left ventricular hypertrophy, while individuals with ACE of 11 genotype did not have a cardiac morphology response to training. These two last studies [45,46] may have implications for which exercise mode will best serve athletes or cardiac patients in terms of modulating cardiovascular function during exercise training.

Despite exercise's general benefit, individual responses to exercise vary [47]. The basis for this is unclear, but there appears to be a strong genetic component [48]. An insertion (I)/deletion (D) polymorphism in intron 16 of the ACE gene has been identified as a potential marker for the differential response to exercise. In the field of hypertension the D allele is associated with significantly higher ACE. In response to exercise, the D allele has been associated with increased muscle strength and power while I allele has been associated with better muscular endurance although data are not entirely consistent. Since both muscle strength and endurance are determinants of physical function in older adults, maintenance of physical function could be related to ACE I/D genotype. However, studies involving younger individuals suggest that a genotype effect would be seen primarily in response to high physical activity levels [49].

Conclusions

Exercise may stimulate genetic adaptations through epigenetic that, in turn, modulate the link between the environment, human lifestyle factors, and genes. The health benefit of physical exercise, especially on a long term and strenuous basis, has a positive effect on epigenetic mechanisms and ultimately may reduce incidence and severity of disease. The interaction of genes and exercise in modifying health status occurs at multiple levels. At the molecular level, the direct mechanism by which exercise alters gene expression involves activation of signal transduction pathways resulting in enhanced transcription of messenger RNA and subsequently increased translation into protein [50]. The impact of exercise on genetics in elderly appears to have multiple influences. Its positive effect on gene expression must be combined with effective training programs and favorable lifestyle habits for optimal aging success. As health and fitness practitioners, it is good to appreciate the interrelation that genetics plays in the aging process and the positive role that aerobic exercise have. However, the best message is that regardless of hereditary, regular participation in aerobic training will lead to remarkable improvements and enhancement of life quality. Environmental factors including physical exercise have been shown to have a beneficial influence on epigenetic modifications, such as histone modifications and DNA methylation, attenuate age-related declines in physical function, thus, actually slow the aging process. With increased age, telomeres-sequences of DNA found at the end of a chromosome that protect chromosomes from damage, get shorter which mean more weary cells. However, the telomeres of participants who exercised more in their leisure time are longer than the telomeres of people who did not get

as much physical activity. However, variability exists in elderly responsiveness to training, in the insertion (I allele) or deletion (D allele). This polymorphism is known to influence a variety of physiological adaptations to exercise. It seems that ACE I/D genotype appears to play a role in modulating functional responses to exercise training in the elderly.

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